

REMARKS

Introductory Comments

Applicant respectfully requests reconsideration of this application in view of the foregoing amendments and the following remarks.

Upon entry of the amendments, claims 13-24 will remain pending, with claim 14 being withdrawn from consideration. No claims are being added or canceled. Claims 13 and 23 are being amended, without introducing new subject matter into the application.

The Claims Comply with the Enablement Requirement of 35 U.S.C. § 112

Claims 13 and 15-22 were rejected as allegedly failing to comply with the enablement requirement of 35 U.S.C. § 112, first paragraph. The rejection was specifically based on three assertions: (1) there is insufficient evidence that the anti-HM1.24 antibody employed in the claims binds to the polypeptide encoded by SEQ ID NO:1, (2) there is insufficient evidence that the antibodies employed in the claims could bind T lymphocytes, and (3) there is insufficient evidence that the claimed method could inhibit lymphocyte activation without killing the lymphocyte. Applicants respectfully traverse the rejection, and rebut each of the three assertions below.

In contrast to the first assertion, there is ample evidence within the specification that the anti-HM1.24 antibody binds to the polypeptide encoded by SEQ ID NO:1. Reference Example 3 of the application describes work in which SEQ ID NO:1 was identified from the cloning of cDNA that encodes HM1.24 antigen protein. In that example, total RNA from the human multiple myeloma cell line KPMM2 was prepared and used to construct a cDNA library, which was transduced into an *E. coli* strain. Plasmid DNA was obtained from the *E. coli* and transfected into COS-7 cells. After culturing of the COS-7 cells, an anti-HM1.24 antibody was used to pan for and isolate cells expressing HM1.24. Plasmid DNA was recovered from those isolated cells and sequenced. The nucleic acid sequence obtained was that of SEQ ID NO:1. Thus, a clear indication exists in the specification that the anti-HM1.24 antibody binds to the polypeptide encoded by SEQ ID NO:1.

The nexus between SEQ ID NO:1 and the anti-HM1.24 antibody is further confirmed by the work of Ohtomo et al., Biochem. and Biophys. Res. Comm., 258: 583-591 (1999) (of record). Additionally, Applicant notes that a hybridoma that produces the antibody described in the present specification is on deposit as FERM BP-5233 and is available to the public according to the terms of the Budapest Treaty.

In contrast to the second assertion, there is ample evidence that the antibodies employed in the claims can bind T lymphocytes. This fact does not conflict with the report of Goto et al., Blood, 84(6): 1922-1930 (1994) (of record). The specification shows binding of HM1.24 antibody to T lymphocytes in Figs. 2 and 3. These figures show the results of work done in Example 3. As can be seen from Fig. 2, although HM1.24 antibody does not bind to T lymphocytes without blast formation (as shown by the plot of the no-PHA stimulation), HM1.24 antibody increasingly binds to T lymphocytes with blast formation (according to the expression of the antigen recognized by the HM1.24 antibody). As can further be seen from Fig. 3, the stimulation to expression of HM1.24 accompanying the blast formation was constant.

Applicant's results do not conflict with those of Goto et al. The observation by Goto et al. that HM1.24 antibody did not bind to T cells can be understood as resulting from a lack of blast formation in the Goto et al. work. This conforms with the results set forth in the present application for no-PHA stimulation. Thus, there is no discrepancy between the results of Goto et al. and the results set forth in the present application. The presently claimed invention relates to a novel finding regarding the binding of HM1.24 antibody to T cells, specifically that HM1.24 antigen is highly expressed in T cells with blast formation and that the high expression is not transient. Goto et al. simply did not identify the relationship between HM1.24 antibody binding and the activation of T cells.

In contrast to the third assertion, there is sufficient evidence that the claimed method can inhibit lymphocyte activation without killing lymphocytes. The Office's contrary assertion ignores that antibodies used in the Examples of this application have a different origin than antibodies used in the references cited to show the killing of lymphocytes. It is well known in the art that effector cells in the peripheral blood recognize and bind to

antibodies via Fc receptors. Thus, the binding and ADCC activities of effector cells (mainly NK cells) in relation to a chimeric antibody having human Fc sequences, a humanized antibody or a human antibody is higher than the binding and ADCC activities of effector cells in relation to a mouse antibody. In EP 0960936, cited by the Office, a humanized antibody was used. Likewise, the Stites et al. reference cited by the Office refers to ADCC via a human antibody. By contrast, the Examples of the present application employ a mouse IgG2a isotype anti-HM1.24 antibody.

Also, the ratio of effector cells to target cells is different in Examples of the present application and the cited references. Although the binding activity of effector cells to mouse antibody is significantly lower than the binding to antibodies having human Fc sequences, it is known in the art that effector cells can weakly recognize mouse IgG2a antibodies. Kipps et al., J. Exp. Med., 161, 1-17, 1985 (attached as Exhibit 1) discusses in detail that the ratio of effector cells to target cells impacts mouse IgG2a-mediated ADCC activity by human peripheral lymphocytes. Fig. 7 of the Kipps reference depicts the effect of effector cell ratio. In the reference cited by the Examiner, the ratio of effector cells to target cells was 50:1 (EP 0960936). By contrast, in Examples of the present application, the ratio of effector cells to total cells in peripheral blood was not changed. The percentage of NK cells in peripheral blood is believed to be about 10 to 15%, and it is known in the art that ADCC activity with 10 to 15% effector cells is negligible. This indicates that in Examples of the present application, inhibition of lymphocyte activation by anti-HM1.24 antibody was achieved without killing lymphocytes.

Additionally, in the examples of the present application that relate to inhibiting T lymphocyte activation, a Cellect Humm T cell Kit (manufactured by Biotex) was used to purify T cells from human peripheral blood. Thus, the cell preparations used were essentially free of effector cells (such as NK cells), meaning that the inhibition of T lymphocyte activation was obtained without ADCC activity.

Because the assertions on which the enablement rejection was based are incorrect, Applicants respectfully request withdrawal of the rejection.

The Claims Comply with the Written Description Requirement of 35 U.S.C. § 112

Claims 13 and 15-22 were rejected as allegedly failing to comply with the written description requirement of 35 U.S.C. § 112, first paragraph. In particular, the Office stated that the specification does not support the requirement for inhibiting lymphocyte activation *without killing lymphocytes*.

Applicant does not acquiesce in the rejection. Nevertheless, the rejection is now moot, as the claims no longer contain the explicit recitation “without killing lymphocytes.” As described above, however, ADCC activity and effector cells are not involved in the claimed uses or activities. Thus, the method actually is effected “without killing lymphocytes.”

Because the written description rejection is now moot, Applicant respectfully requests its withdrawal.

The Claims Comply with the Definiteness Requirement of 35 U.S.C. § 112

Claims 13 and 15-24 were rejected as allegedly failing to comply with the requirement of 35 U.S.C. § 112, second paragraph, that claims particularly point out and distinctly claim the invention. In particular, the Office stated that SEQ ID NO:1 comprises a DNA sequence, and not an amino acid sequence as implied by the claims.

In view of the foregoing claim amendments, the rejection is now moot. The claims now recite that the antibody binds to a “protein having an *amino acid sequence encoded by the nucleotide sequence* set forth in SEQ ID NO: 1” (emphasis added). Thus, it is clear in the claims that SEQ ID NO:1 contains a nucleotide sequence. Accordingly, Applicant requests withdrawal of the rejection.

The Claims are Patentable over the Asserted Prior Art

Claims 23-24 were rejected under 35 U.S.C. § 103(a) as allegedly being obvious over U.S. Patent No. 5,298,420 in view of Goto et al., Blood, 84(6): 1922-1930 (1994). Applicants respectfully traverse the rejection; the combined references neither teach nor suggest the claimed invention.

The '420 patent relates to isotype-specific reduction/elimination of B cells. According to the patent, so-called "migis" epitopes can be targeted for that purpose. Migis epitopes are membrane-bound immunoglobulin isotype-specific extracellular epitopes of B cell membrane-embedded antibodies. Not all B cell surface epitopes are migis epitopes. The teachings of the '420 patent do not extend beyond targeting migis epitopes, and the patent does not suggest that any B cell surface epitope can be exploited for reducing/eliminating B cells.

Goto et al. reported a monoclonal antibody (anti-HM1.24 antibody) that was obtained by immunizing mice with human myeloma cells. When the anti-HM1.24 antibody was administered to a mouse transplanted with human myeloma cells, the antibody accumulated in tumor tissues in a specific manner. Goto et al. did not teach the use of HM1.24 antibodies to treat multiple myeloma. Rather, they stated only that HM1.24 protein "represents a specific marker of late-stage B-cell maturation" and suggested that HM1.24 "potentially serves as a target antigen for immunotherapy of multiple myeloma." No evidence in the Goto et al. reference supports such a use of anti-HM1.24 antibodies. Moreover, Goto et al. neither taught nor suggested that the administration of anti-HM1.24 antibodies, *per se*, could inactivate B cells. Goto et al. also did not identify HM1.24 as a "migis" antigen.

The combination of the '420 patent and the Goto et al. reference fails to teach or suggest the claimed invention. The teachings of the '420 patent do not extend beyond migis antigens, and Goto et al. did not identify HM1.24 as being a migis antigen. Even if the '420 patent teachings could be generalized beyond migis antigens (which they cannot), there was no suggestion that the binding of *any* antibody to *any* lymphocyte surface epitope inactivates the lymphocyte. As the Office has pointed out during prosecution, biology and physiology are unpredictable arts. Without benefit of the inventor's work, therefore, one skilled in the art would not have had a reasonable likelihood of success for using an anti-HM1.24 antibody to treat a disease associated with lymphocyte activation. The inventor was the first to show with any reasonable certainty that anti-HM1.24 antibodies actually do inhibit lymphocyte activation.

Because the cited art did not teach or suggest the claimed invention, and because no likelihood of success existed for practicing the invention before Applicant's work, Applicant respectfully requests withdrawal of the rejection.

Concluding Remarks

This application is now in condition for allowance, and Applicant respectfully requests favorable reconsideration of it.

If the Examiner believes that an interview would advance prosecution, he is invited to contact the undersigned attorney by telephone.

The Commissioner is hereby authorized to charge any additional fees that may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extensions under 37 C.F.R. § 1.136 and authorizes payment of any extension fees to Deposit Account No. 19-0741.

Respectfully submitted,

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